REMARKS

Claims 1, 4, 7-9 are now pending in the application. Minor amendments have been made to the claims to simply overcome the objections to the specification and rejections of the claims under 35 U.S.C. § 112. The amendments to the claims contained herein are of equivalent scope as originally filed and, thus, are not narrowing amendments. Claim 9 is a new claim to subject matter contained in the specification as originally filed but not previously claimed. Support for the new claim can be found throughout the specification as originally filed, in particular as described on page 2, lines 2-8. The Examiner is respectfully requested to reconsider and withdraw the rejection(s) in view of the amendments and remarks contained herein.

REJECTION UNDER 35 U.S.C. § 112 SECOND PARAGRAH

Claims 1, 4, 7, and 8 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point and distinctly claim the subject matter which Applicant regards as the invention. This rejection is respectfully traversed.

From the outset, Applicants respectfully submit that the presently amended Claims 1 and 4 and claims dependent thereon are fully enabled under 35 U.S.C. § 112, second paragraph.

H. Claim 1 is rejected for allegedly being indefinite due to the lack of clarity as to how existing characteristics of a compound might modulate pharmacological activity of said compound. (Action at page 3). In addition, the Action states that the claim preamble is not clear as to which one of the plurality of characteristics being

determined, displayed and is addressed as modulating pharmacological activity of a compound.

Without acquiescence to the Action's allegations of indefiniteness, Applicants have amended the preamble of Claim 1 to focus on specific embodiments of the present application. The amended preamble of Claim 1 recites: "A computer based method for generating a three-dimensional quantitative structure-activity relationship of a compound, the compound derived from a plurality of molecules each having a related pharmacological activity and visually displaying a region of the compound in which altering one or more physiochemical characteristics of said region can predict a change to said pharmacological activity of said compound, the method comprising…."

Applicants respectfully submit that the physicochemical characteristics or properties being described are defined in the specification as filed on page 1, lines 19 and spanning page 2, lines 1-6 and on page 49, lines 11-16. The physicochemical characteristics being extracted from the present methods include hydrophobic, steric and electrostatic interactions that affect the biological activity of the compound or molecule as measured by one or more pharmacological activities (e.g. binding constants, association constants, inhibition constants, inhibitory concentration at 50% inhibition of the target (IC_{50}) and the like). This can include the effects of steric, electrostatic and hydrophobic (lipophilic) characteristics of a molecule with respect to its binding affinity to a target biomolecule, for example, a receptor or other protein. The physicochemical characteristics of a compound as provided in the originally filed application can and most certainly do affect the binding affinities of that compound with its cognate target. In some cases as shown by the examples of the present methods

(see for example in Figure 10) compounds that have altered regions designated in one color by introducing a substitution group that is sterically demanding will enhance activity of the compound. The enhanced activity can include for example, a higher binding association constant. Whereas other colored regions in the same compound indicate that replacing the group of other colored atoms with a sterically demanding substitution will result in a decrease in the activity of the compound.

Applicants also traverse the second point of indefiniteness with respect to one or more physiochemical characteristics of the compound being capable of affecting the pharmacological activity of said compound. The physicochemical characteristics can include steric, electrostatic and hydrophobic interactions that can each independently and in combination affect the pharmacological activity of the compound. The effect can also be a positive or enhancing effect towards the activity or it may be a negative or diminishing effect on the activity of the compound.

I. Claim 1 is presently rejected as being indefinite for allegedly not making clear which "plurality of molecules" is being superposed, and whether these molecules have any relationship to each other.

Applicants have amended Claim 1 process A to recite: "a process A of superposing a three-dimensional spatial arrangement of atoms of [[a]] <u>said</u> plurality of molecules using Cartesian three-dimensional x, y, and z atomic coordinates in a virtual space;" As such, there is not a strict structural requirement for each of the plurality of molecules being superposed. Each of the plurality of molecules can have a predetermined pharmacological activity being correlated in the present methods. For

example, the molecules being superposed can be ligands for a biologically active protein, as illustrated in the application by human corticoidsteroid-binding globulins as shown in Table 1 of the present application. The correlated and evaluated pharmacological activity is the binding affinity to human corticoidsteroid-binding globulins. The plurality of molecules being used in the method have in common a predetermined pharmacological activity. The plurality of molecules can include conformers of one molecule and can also include different molecules differing in structure but that also possesses a common predetermined pharmacological activity.

J. Claim 1 is presently rejected as being indefinite for allegedly not making clear in process C how atoms may have "interaction" with such "represented points". (Action at page 3). Specifically, the Action states that "it is not clear how an atom and a "represented point" may have such interactions as steric, electrostatic, hydrogen-bonding or hydrophobic"

Applicants respectfully submit that the calculation of steric, electrostatic and hydrophobic interactions between each atom of the superposed plural molecules and a represented point can be determined using an evaluation function, for example a Gaussian formula with respect to steric and electrostatic interactions. FLEX can be used for calculating hydrophobic interactions between the represented point and each atom of the superposed atom. (See Application on page 30, lines 1-19). Other evaluation functions can be used to determine steric, electrostatic hydrophobic interactions. Steric and electrostatic interactions (also stated as potential energy fields) can be computed between a probe atom placed in a lattice intersection and a molecule calculated for all

lattice intersections as described in traditional CoMFA procedures as described by Cramer et al., U.S. Patent No. 5,025,388. Instead of using a probe atom, the present application directs the use of a represented point, which is a different point of reference within the molecule being analyzed and is determined using a different method when compared to traditional CoMFA. Each of the interactions determined for each of the atoms in the molecule when compared to a represented point is then entered into the table illustrated in FIG. 3. Moreover, the present application does not use potential energies expressed as kcal/mol as used in CoMFA but rather uses dimensionless values as in the CoMSIA method. The interactions are not described as kcal/mol as in CoMFA but rather interactions are described in different units, for example as logP (Application at page 38, lines 9-16) The interactions calculated between a represented point and atoms of a superposed molecule in the present application are also dimensionless. The steric and electrostatic interactions in the present application are calculated using similarity indices derived from SEAL type Gaussian evaluation functions and indicator variables. (See specification discussing the method for the various interaction calculations on page35, Section 1B and Section 1D on page 36) The application also states that the steric interactions can be determined between a represented point and the atoms of a superposed molecule using the method described in Kotani, T. et al., J. Chem. Inf. Comput. Sci., 2002, 42, 58-63. FLEX another method for fast ligand superposition is described in the application which can be used for calculation of hydrophobic interactions. All of these methods to calculate the interactions (steric, electrostatic and hydrophobic) between the represented point(s) and

the superposed molecules are thoroughly described in the specification as filed, for example at pages 35-37. A specific method for

K. Claim 1 is presently rejected as being indefinite for allegedly not making clear in process D what is the significance of interaction between atoms and an arbitrary "represented point". (Action at page 4).

Applicants respectfully submit that the determination of the "represented point" is not arbitrary. Rather, the "represented point" is determined using first a cluster analysis of superposed molecules to generate an atomic coordinate model. From the atomic coordinate model, the spatial distances between atoms are compared and the pair of atoms having an interatomic distance equal than or less than a threshold value are removed from the virtual space. The weighted average coordinates of the coordinates of these two atoms are calculated and replaced with a represented point.

After the final atomic coordinate model having all of the represented points charted and calculated, then the significance of the interactions between the plurality of atoms of the superposed molecule and the represented points found in the atomic coordinate model is directly compared to the pharmacological activity of the superposed molecule as given by the table in FIG. 3. The data representing the interactions determined using the evaluation functions are then entered into the calculation of the structure-activity relationship formula using a partial least squares (PLS) regression method. The use of the structure-activity relationship formula is necessary to calculate which portion or portions of the compound thus analyzed contributes to enhanced or reduced pharmacological activity of the compound (e.g. binding affinity to a receptor).

The results of the PLS calculation can then be used to determine an activity prediction formula. The activity prediction formula can be used to graphically associate the magnitude and sign of the association between the interaction change at each atomic position and the pharmacological activity of the compound or molecule.

The correlation components generated using the regression analysis of step D of Claim 1 refers to the correlation of a component (such as an interaction value or descriptors) to an object variable such as a pharmacological activity common to all compared molecules. The regression thereby provides a regression equation. The use of the PLS regression analysis is akin to the PLS regression method described in Cramer et al., U.S. Patent No. 5,025,388. The determination of the activity prediction formula can be derived after the interaction calculations have been determined and entered into a PLS analysis. Then the activity prediction formula is calculated after the PLS method derives coefficients for each of the interactions for every atom measured. The solutions to the equations found by PLS is the set of values of the coefficients of the interaction terms derived from a 3D-QSAR table. The R^2 value is calculated in an iterative fashion to determine the how well the equation predicts the data obtained. As explained in the original specification on page 30, the number of PLS components used to calculate an activity prediction formula can be determined using the "leave one out" method. This method is described in Cramer et al., U.S. Patent No. 5,025,388, at cols. 14-15. The sign and magnitude of the calculated component coefficient is indicative of the type of effect (negative effect or positive effect on activity) and the strength of association between the types of interaction (steric, electrostatic and hydrophobic) of those atoms and the pharmacological activity of the entire molecule. The graphical plot

in three dimensions of the coefficient's values, *i.e.* the activity prediction value (atom by atom) results in a display of the regions in space of the groups of atoms most responsible for predicting changes in molecular pharmacological activity.

The Examiner's contention that a molecule's pharmacological activity cannot be attributed to a change made to an atom, since only molecules can effect a biological activity is well taken. However, the Applicants respectfully submit, that when the results of the present methods are viewed for example in FIGs. 10-45, it can be seen that steric, or electrostatic or hydrophobic changes to groups of atoms contribute to the observed molecule's pharmacological activity and not a single atom.

L. Claim 1 is presently rejected as being indefinite for allegedly not making clear in process E how to generate the "activity predicting value". (Action at page 4). Claim 1 is also rejected for allegedly failing to make clear how an activity is assigned to each and every atom of each and every molecule.

The Applicants respectfully submit that the data generated by the instant PLS method is treated as described for conventional 3D-QSAR. The specification states:

> "According to the PLS method, a value called a "component" correlated with an object variable (such as a pharmacological activity value) is extracted from among a number of descriptors, and a regression equation is formed. The "component" is very similar in nature to a principal component which is computed in principal component analysis, and where plural components are extracted, they are orthogonal to each other. Due to this, it is possible to frame an activity prediction formula from data containing a very large number of variables, e.g., CoMFA data. The number of PLS components is determined by the reliability evaluation method called "Leave-one-out" method, and with the number of components necessary to form the most

reliable activity prediction formula, an activity prediction formula is made."

The method for determining the activity prediction value is the same as the method for determining the equation coefficient for each column of the data table shown in FIG. 3 of the originally filed application. The methods used to derive the equation or solution coefficients using a CoMFA table are known to those of ordinary skill and is described in Cramer et al., U.S. Pat. No. 5,025,388, particularly described at cols. 15-17. As used herein, the equation coefficients a and b derived from the structure-activity relationship formula shown in FIG. 3 of the specification as originally filed can be equated to the activity prediction value after the PLS regression and cross-validation procedure has been performed on the acquired CoMFA data table as also shown in FIG. 3 using the method steps described in the present application. The equation coefficients can be used in reverse to obtain the steric, electrostatic and hydrophobic interaction quanta for every atom in the compound or molecule to reveal those regions of the molecule or compound which are associated with increased or decreased pharmacological activity.

M. Claim 1 is presently rejected as being indefinite for allegedly not making clear in process C, step B2 whether the atomic distances in step B2 are calculated for atoms of the same molecule or different molecules. (Action at page 4). The amended process C, step B2 recites: a second process B2 of calculating interatomic distances between each atom and other atoms superposed and identifying the shortest interatomic distance among thus calculated interatomic distances and two atoms

constituting the shortest interatomic distance;". Hence from the amended claims and the specification as originally filed (specifically, on page 27, lines 13-19) the interatomic distances are calculated for both atoms within a molecule and between atoms superposed as shown in FIG. 3.

The following rejections under 35 U.S.C. § 112, second paragraph are being maintained from the previous Office Action dated April 14, 2008.

A. Claim 1 stands rejected due to he alleged lack of clarity of the claim language for failing to recite a final process step, which agrees back with the preamble. (Action at pages 4 and 5).

Applicants have amended the preamble and last method step reciting: a process E of assigning an activity prediction value to each atom of said plurality of molecules and displaying said activity prediction value overlayed on said compound on a graphical display…." Applicants respectfully submit that the amended preamble is directed to a computer based method for generating a three-dimensional quantitative structure-activity relationship of a compound, the compound derived from a plurality of molecules each having a related pharmacological activity and visually displaying a region of the compound in which altering one or more physiochemical characteristics of said region can predict a change to said pharmacological activity of said compound, the method comprising". Both the preamble and the last method step of Claims 1, 4 and 9 recite displaying a graphical output of a compound and a region therein displaying activity prediction values.

As such, the activity predicting values displayed is indicative of a region in which altering one or more physicochemical characteristics of the region displaying the activity prediction values can predict a change to a pharmacological activity of the compound.

F. Claim 1 stands rejected for allegedly being indefinite for failing to clarify how interactions between atoms and points can be calculated. (Action at page 5). This rejection is equivalent to the new rejection under item J. Applicants respectfully submit that the calculation of steric, electrostatic and hydrophobic interactions between each atom of the superposed plural molecules and a represented point can be determined using an evaluation function after cluster analysis, for example a Gaussian formula with respect to steric and electrostatic interactions, molecular similarity evaluation method for steric interactions and FLEXS can be used for calculating hydrophobic interactions between the represented point and each atom of the superposed atom. (See Application on page 30, lines 1-19).

The citation of Claim 3 in this rejection is moot considering that Claim 3 was cancelled in the previous response to the Office Action dated April 14, 2008.

G. Claim 1 stands rejected as allegedly being indefinite for failing to clarify how the interactions are being analyzed.

Applicants respectfully submit that the specification as originally filed provides for adequate description of how the interactions between each atom of the superposed plural molecules and a represented point can be determined using an evaluation function after cluster analysis, for example a Gaussian formula with respect to steric and

electrostatic interactions, molecular similarity evaluation method for steric interactions and FLEXS can be used for calculating hydrophobic interactions between the represented point and each atom of the superposed atom. (See Application on page 30, lines 1-19).

Accordingly, Applicants respectfully request that the present rejection of independent Claims 1 and 4 and Claims 7 and 8 dependent thereon under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 112 FIRST PARAGRAH

Claims 1, 4, 7, and 8 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed.

A. Independent Claims 1 and 4 are rejected for allegedly introducing new matter, specifically for introducing the phrase "assigning activity prediction value to each atom". (Action at page 6).

Applicants respectfully submit that the assigning an activity prediction value to each atom is equivalent to deriving the coefficients from the solution provided in the structure-activity relationship formula shown in FIG. 3, wherein the activity (activity prediction value) can be calculated after performing the partial least squares regression along with cross-validation of the resultant coefficients derived. One of ordinary skill in the art would readily understand how to assign an activity prediction value once the

structure-activity relationship formula is calculated. One of ordinary skill in the art could be guided by the teachings of Cramer et al., U.S. Patent No. 5,025,388 to plot the activity prediction values, for example by multiplying the field descriptor values for each atom of the compound of interest by the structure-activity relationship formula coefficients (shown in FIG. 3) and summing the results.

B. Claims 6 and 7 are rejected for allegedly introducing new matter into the claim reciting "rapid molecular superstition" and "indicated variables" as embodiments of "evaluation formulas". (Action at page 6-7).

Applicants respectfully submit that support for the various embodiments of evaluation formulas recited in the amended Claim 7 exists on pages 35 and 36 of the originally filed specification. A minor typographical error was corrected in the presently amended Claim 7 to recite "rapid molecular superposition evaluation" as a method to calculate the relative contributions of the steric, electrostatic, hydrogen bonding and hydrophobic interactions between the represented point and atoms of the tested molecule.

Claim 6 was previously cancelled as requested by the Examiner, and as such, this rejection is moot with respect to Claim 6.

Accordingly, Applicants respectfully request that the present rejection of Claims 1, 4, 6 and 7 under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 101/112-1

Claims 1, 4, 7, and 8 stand rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility due to its not being supported by either specific and/or substantial utility or a well established utility. This rejection is respectfully traversed.

From the outset, Applicants respectfully submit that the claims as amended provide specific, substantial and well established utility.

Applicants respectfully resubmit that the computer implemented methods of Claims 1 and 4 result in the determination and subsequent visual representation of regions of molecules that impact the pharmacological or biological activity of said molecule. The presently amended Claim 1 recites:

> A computer based method for generating a three-dimensional quantitative structure-activity relationship of a compound, the compound derived from a plurality of molecules each having a related pharmacological activity and visually displaying a region of the compound in which altering one or more physiochemical characteristics of said region can predict a change to said pharmacological activity of said compound, the method comprising:
>
> a process A of superposing a three-dimensional spatial arrangement of atoms of said plurality of molecules using Cartesian three-dimensional x, y, and z atomic coordinates in a virtual space;
>
> a process B of performing cluster analysis of the atomic coordinates of said atoms of said plural molecules thus superposed in said virtual space and thereby generating represented points;
>
> a process C of calculating interactions selected from the group consisting of steric interactions, electrostatic interactions, hydrophobic interactions and combinations thereof between the atoms of said plural molecules thus superposed and said represented points using an evaluation function;
>
> a process D of statistically analyzing said interactions using regression analysis to generate a plurality of correlation components between said calculated interactions

> and said pharmacological activity of said molecules and forming an activity prediction formula; and
>
> a process E of assigning an activity prediction value to each atom of said plurality of molecules and displaying said activity prediction values overlayed on a region of said compound on a graphical display….

Applicants respectfully submit that the present methods provide for methods for identifying and predicting regions of a molecule that upon modification, can effect a change to the pharmacological or biological activity of the molecule. Applicants respectfully submit that there is a transformation of physical data in one form to data that is useful and possesses credible utility in a different form and which is displayed for a user. Such transformation of physical data is eligible as patentable subject matter.

> In contrast, we held one of Abele's dependent claims to be drawn to patent-eligible subject matter where it specified that "said data is X-ray attenuation data produced in a two dimensional field by a computed tomography scanner." Abele, 684 F.2d at 908-09. This data clearly represented physical and tangible objects, namely the structure of bones, organs, and other body tissues. **Thus, the transformation of that raw data into a particular visual depiction of a physical object on a display was sufficient to render that more narrowly-claimed process patent-eligible**.
>
> **We further note for clarity that the electronic transformation of the data itself into a visual depiction in Abele was sufficient; the claim was not required to involve any transformation of the underlying physical object that the data represented.** We believe this is faithful to the concern the Supreme Court articulated as the basis for the machine-or-transformation test, namely the prevention of pre-emption of fundamental principles. So long as the claimed process is limited to a practical application of a fundamental principle to transform specific data, and the claim is limited to a visual depiction that represents specific physical objects or substances, there is no danger that the scope of the claim would wholly pre-empt all uses of the principle.

> Citing *In re Bilski*, 88 USPQ2d, 1385, 1397 (Fed. Cir. 2008) (emphasis added).

Under the new standard promulgated by the Federal Circuit, the Applicants respectfully assert that the structure of the various chemical molecules being examined are chemical structural data which is a tangible and physical object as exemplified in Abele and Bilski *supra*. The data representing the chemical structures are then transformed to a depict graphically a representation of a chemical compound structural data illustrating regions of the chemical structure that may be manipulated to effect a change in the chemical structure's pharmacological activity by altering the physicochemical interaction between the atoms in the region thus identified. Transformation of data of a physical and tangible object (i.e. chemical molecules sharing a common pharmacological activity) into a particular visual depiction is sufficient to render the methods of Claims 1, 4 and 9 and claims dependent thereon patent - eligible. Again, Applicants point to the Federal Circuit's latest interpretation that the transformation of the data representing a physical object must be considered as the subject of transformation and not necessarily the underlying physical object that the data represented.

The methods described in various embodiments of the present application circumvents the need to chemically synthesize hundreds to thousands of molecules and performing empirical measurements on each to determine the activities of the newly designed molecules. The present methods enable a chemist to predict the likely activity for the shape and physicochemical characteristics of a proposed molecule specified by the chemist without having to synthesize or isolate said molecule *de novo*. This circumvention of effort has a real world utility and has been found to possess specific

and/or substantial activity or a well established activity by the issuance of patents 5,025,388, 7,329,22 and 7,184,893 all to Cramer et al.

Specific examples of utility can include the elimination of large data sets representing lattice points in order to obtain an accurate molecular 3D quantitative structure-activity relationship. (See specification at page 8, lines 22-25, page 9, lines 1-9 and page 18, lines 4-12). Other examples of specific and/or substantial utility embodied in the amended claims can be found on page 11, lines 2-14, which include broader computation of structure-function activity using a wider array of computer resources, elimination of singularity and cut-off associated with other modeling processes and overcoming the difficulty associated with modeling the structure-activity of difficult atom types.

Claims 1, 3, 4, and 6 stand rejected under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific and substantial asserted utility or a well established utility. Specifically, the Action alleges that it is not clear how an existing characteristics of a compound might modulate (in an unidentified way) a pharmacological activity of said compound. Further, the Action alleges that it is not clear how an "activity prediction value to each atom" in multiple molecules allows determining and displaying physicochemical characteristics of compound… which modulates pharmacological activity of the compound. This rejection is respectfully traversed.

The amended Claims 1 and 4 recite methods that can be applied for generating a three-dimensional quantitative structure-activity relationship of a compound, the

compound derived from a plurality of molecules each having a related pharmacological activity and visually displaying a region of the compound in which altering one or more physiochemical characteristics of the region can predict a change to the pharmacological activity of the compound. With respect to the regions identified by the present methods that can predict a change in pharmacological activity, these regions are calculated using the inventive methods steps described in Claims 1, 4 and 7-9. These regions are identified and are graphically displayed so that a chemist can change a certain interaction (i.e. replace one or more atoms that increase the size of the region sterically, or add an atom or group of atoms that change the electronegativity of the region, or increase or decrease the hydrphobicity of the region) that will result in a change of the pharmacological activity of the molecule. The method analyzes the effects of the various interactions measured (steric, hydrophobic, hydrogen-bonding and electrostatic) and compares these interactions to the pharmacological activity obtained by the analyzed molecule. By calculating an activity prediction value and assigning such a value to the atoms of a compound, and graphically displaying such values as represented in Figures 10-45 in the present application, a chemist can readily see which atoms in specific regions can impact the pharmacological activity if a change to the identified interaction is made. The utility is evident immediately when looking at the results of the claimed methods. For example, Figure 10 represents a compound modeled after the steroid derivatives that bind to human-corticosteroid-binding globulins using the methods of Claim 1. A chemist can readily ascertain valuable information that graphically represents regions of the molecule that will enhance or weaken the pharmacological activity of the compound if steric interactions are modified at the

identified regions. There is no further need to research, the results thus obtained are useful, concrete and complete. The identified regions determined using the present embodiments enables a chemist to predict the likely pharmacological activity of a compound based on the shared activities of the molecules used to model the compound. The activity prediction values can be calculated from the structure-activity relationship formula and can be applied to predict the effects of any of the interactions modeled using the component coefficients derived from the structure-activity relationship formula.

Methods for generating a three-dimensional quantitative structure activity relationship and visually displaying the relationships to a user have been found to have specific and substantial asserted utility or a well established utility. See U.S. Patent No. 7,329,222.

Claims 3 and 6 have been previously cancelled, and thus rejections under 35 U.S.C. § 101 as to these claims are moot.

Accordingly, Applicants respectfully request that the present rejection of Claims 1, 4, and 7 under 35 U.S.C. § 101, be reconsidered and withdrawn.

Claims 1, 4, 7, and 8 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention. This rejection is respectfully traversed.

Applicants respectfully submit that Claims 1 and 4 are fully enabled by the specification as filed. The methods for graphically displaying of regions of a compound

that can affect the pharmacological activity of the compound by alteration of a specific interaction, such as, steric, electrostatic and hydrophobic in the identified regions of the compound have been adequately described in the originally filed application. Applicants respectfully submit that the claimed invention fully supports a credible utility and/or a well established utility as described above. One of ordinary skill in the art could readily model a series of molecules or identify and design new molecules having enhanced pharmacological activity by implementing the methods embodied by the pending claims.

Accordingly, Applicants respectfully request that the present rejection of Claims 1, 4, and 7 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

REJECTION UNDER 35 U.S.C. § 101 (NON-STATUTORY INVENTION)

Claims 1, 4, 6, and 7 stand rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. This rejection is respectfully traversed.

From the outset, Applicants respectfully submit that the amended claims produce a useful, tangible and concrete result relating to quantitative structure-activity relationships in a molecule or unknown compound.

Applicants respectfully submit that the claims of the present application are directed to statutory subject matter without the need to perform an analysis under the judicially created exceptions. Assuming arguendo that the present method claims fall under the judicial exception which the Applicants do not concede, Applicants respectfully submit that the claims in the present application are directed to an invention that produces a result

which is concrete, tangible and useful, and in support thereof present the following remarks.

Initially, as a beginning point in the analysis the Action summarizes the claims as follows:

"The instant claims seem to be directed to calculation of an abstract interactions between points in space with atoms of molecules. Such calculation results in an activity prediction value" related to each atom. As atoms, unlike molecules, do not have "activity", this is not viewed as a "real world" practical result." (Action at page 9).

Applicants respectfully disagree with the above recitation. The end result of the present embodiments is the graphical display of all of the activity-prediction values. Process E of Claims 1 and 4 recites: "process E of assigning an activity prediction value to each atom of said plurality of molecules and displaying said activity prediction values overlayed on a region of said compound on a graphical display…"

First, the Applicants respectfully note that the calculation of regions of a compound having areas in which atoms contained therein may alter the pharmacological activity of the compound if one or more atoms are altered is determined on a per atom basis, but the useful result displays one or more regions of molecules not an individual atom having a prediction value. (See Figures generally, indicating regions of the molecule involving a plurality of atoms affecting the activity e.g. pharmacological activity of the compound). The amended claims recite displaying activity prediction values overlayed on a region of the compound which necessarily includes more than one atom. Furthermore, replacement of a single atom in a molecule can have an effect on that molecule's ability to bind to a target. Although molecules

may exhibit activity, the composition of the molecule, i.e. it's atoms and their spatial arrangement determines what activity that molecule will have.

The steric, hydrophobic and electrostatic interaction between atoms similarly may affect the molecule's pharmacological activity. Hence replacement of one atom in a region of a molecule that may be involved in binding, for example to a receptor, may affect the molecules binding affinity if the atom replaced is electrostatically repulsive to the nearest atom, or the atom's size may impact proper alignment of the binding pocket for that particular molecule. Hence, the activity prediction value although calculated for all of the atoms, it is graphically displayed as a region that may comprise more than one atom capable of exerting a change in pharmacological activity of the entire molecule.

Second, the Action states that the claims do not satisfy the "concrete" prong of requirement for claims directed to judicial exceptions, as it does not seem to be producing the same result if repeated by another person.

"Concrete" requires that there be predictability to the invention. The concreteness of the results thus obtained by the present claims is evident here. Applicants respectfully submit that the Applicants have provided a method of molecular superposition which is faster and non-arbitrary. (See specification at page 3, lines 6-15). The non-arbitrary nature of the superposition is solved by using an evaluation function for example a Gaussian evaluation formula or indicator coefficients. The present application provides that the arbitrariness is alleviated by using an evaluation function. "Molecular superposition which is the first step of 3D QSAR analysis has heretofore used an approach of superposing presumably corresponding atoms with each other or

functional groups with each other between plural molecules to be compared or an approach of sequentially searching for the best superposition by means of an evaluation function (molecular similarity)." (Specification at page 2, lines 2-15).

Applicants respectfully submit that reproducibility is achieved by not relying on the placement of molecules in the form of lattice points as used by conventional CoMFA, but rather, the atomic coordinates of the molecule are determined through cluster analysis which relies of a threshold value as an index. The superpositioning model relies on the extraction of an atomic coordinate model which is not taught in the prior art methods.

Applicants respectfully assert that the problems associated with subjective placement described in the above passage relates to methods that do not employ an evaluation function. The Applicants respectfully submit that the arbitrariness alluded to by the Action is ameliorated in the present embodiments because the cluster analysis and evaluation functions employed in the present methods serve to remove such researcher's subjective effects. There is predictability to the invention. Applicants respectfully submit that the "concrete" criteria is fully met.

Applicants respectfully submit, that Claims 4 and 7 are also similarly eligible as patentable subject matter for the reasons outlined with respect to Claim 1. Claim 6 was previously cancelled and the present rejection applied to Claim 6 is therefore moot.

In summary, Applicants respectfully submit that the claims of the present invention define practical and useful applications and that the inventive methods embodied by the claims produce concrete, useful and tangible results. Accordingly,

Applicants respectfully request that the present rejection of Claims 1, 4, and 7 under 35 U.S.C. § 101, be reconsidered and withdrawn.

CONCLUSION

It is believed that all of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the outstanding Office Action and the present application is in condition for allowance. Thus, prompt and favorable consideration of this amendment is respectfully requested. If the Examiner believes that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (248) 641-1600.

Respectfully submitted,

Dated: Feb. 24, 2009_____

By: /Timothy D. MacIntyre/_____
Timothy D. MacIntyre, Reg. No. 42824

HARNESS, DICKEY & PIERCE, P.L.C.
P.O. Box 828
Bloomfield Hills, Michigan 48303
(248) 641-1600

GAS/FEA/akb

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